

P31376 US

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Campbell et al  
Serial No: 09/117,823  
For: Famciclovir Monohydrate  
Art Unit No: 1611  
Examiner: Mark L Berch

**DECLARATION OF MICHAEL JOHN RAW**

I, Michael John Raw, hereby declare:

1. That I am Michael John Raw of SmithKline Beecham p.l.c., New Frontiers Science Park, Harlow, Essex, CM19 5AW, United Kingdom. I was awarded the degree of Bachelor of Science (Applied Chemistry) in 1984 from Hatfield Polytechnic (now the University of Hertfordshire). Since 1982 I have been employed by Beecham Group p.l.c. and SmithKline Beecham p.l.c. in various capacities relating to analytical chemistry. At the present time, I am an investigator in the Department of Analytical Sciences.

2. I have read and understood the present application US Serial No. 09/117,823 which relates to famciclovir monohydrate. I have also read and understood Harnden *et al*, *J. Med. Chem.*, 1989, 32(8), 1738.

3. I am familiar with the technique of elemental analysis.

4. Elemental analysis involves the oxidation of a known mass of the organic compound to be investigated to form a mixture of carbon dioxide, water and nitrogen oxides. The amount of carbon dioxide produced is measured and this value is mathematically converted to a percentage carbon figure by taking into account the weight of the sample and comparison of the detector response to standards. The carbon dioxide is removed from the system, the amount of water produced is then determined and this measurement is converted to a percentage hydrogen value by a similar process. The water is then removed and the percentage nitrogen in the sample is similarly calculated. The accuracy of this technique is  $\pm 0.4\%$ .

P31376 US

5. The expected elemental analysis for famciclovir monohydrate ( $C_{14}H_{21}N_5O_5$ ) is:

|            |       |
|------------|-------|
| % Carbon   | 49.55 |
| % Hydrogen | 6.24  |
| % Nitrogen | 20.64 |

6. The expected elemental analysis for famciclovir anhydrate ( $C_{14}H_{19}N_5O_4$ ) is:

|            |       |
|------------|-------|
| % Carbon   | 52.33 |
| % Hydrogen | 5.96  |
| % Nitrogen | 21.80 |

7. Harnden *et al.*, in the Experimental Section for production of Compound 14 (last paragraph on page 1741 and paragraph boarding p 1742) provides for percentages of carbon, hydrogen and nitrogen obtained from the elemental analysis of Compound 14 (p 1742, line 8). The analysis demonstrates that Compound 14 produced and tested in accordance therein was (according to p 1741, paragraph 3, line 10) within +/- 0.4% of the calculated values for famciclovir anhydrate (*i.e.*  $C_{14}H_{19}N_5O_4$ ). Harnden *et al.* incorrectly states in the last line of the paragraph boarding p 1742 that Compound 14 has the formula  $C_{14}H_{18}N_5O_4$ . This is obviously a clerical error as Compound 14, according to Scheme 1 on p 1739, clearly has the formula  $C_{14}H_{19}N_5O_4$ . Paragraphs 5 and 6 (above) show that the elemental analysis of famciclovir monohydrate would give a very different percentage of carbon, hydrogen and nitrogen to that of famciclovir anhydrate. The skilled person would therefore recognise that this clearly indicates that Compound 14 is famciclovir anhydrate, and not famciclovir monohydrate as the measured elemental analysis of famciclovir monohydrate would not lie within +/-0.4% of that calculated for famciclovir anhydrate.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of this application or any patent issuing thereon.

Date: 11 December 2000

M. J. Ras.